PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-33153A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/003590	International filing date *(day/month/year)* 01.04.2004	Priority date *(day/month/year)* 02.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/55, A61P25/18		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.10.2004	01.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Paul Soto, R Telephone No. +49 89 2399-7346

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003590

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-14 as originally filed

   Claims, Numbers

   1-21 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003590

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-13 (industrial patentability)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-13 (industrial patentability)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1, 8, 11-17, 19, 21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	16-19, 21; for 1-5 and 20 see separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-13 and 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:

D1: WO 03/042182 A (NOVARTIS PHARMA GMBH ; NOVARTIS AG (CH); SCHMUTZ MARKUS (CH)) 22 May 2003

D2: EP-A-0 751 129 (PORTELA & CA S A) 2 January 1997

D3: AMBROSIO A F ET AL: "MECHANISMS OF ACTION Of CARBAMAZEPINE AND ITS DERIVATIVES, OXCARBAZEPINE, BIA 2-093, AND BIA 2-024" NEUROCHEMICAL RESEARCH, PLENUM PRESS, NEW YORK, US, vol. 27, no. ½, February 2002, pages 121-130, XP009022844 ISSN: 0364-3190

D4: TARTARA A ET AL: "THE PHARMAXOKUNETICS OF OXCARBAZEPINE AND ITS ACTIVE METABOLITE 10-HYDROXY-CARBAZEPINE IN HEALTY SUBJECTS AND IN APILEPTIC PATIENTS TREATED WITH PHENOBARBITONE OR VALPROIC ACID" BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, BLACKWELL SCIENTIFIC PUBL, GB, vol. 36, no. 4, 1 October 1993, pages 366-368, XP000601378 ISSN: 0306-5251

D5: DIETRICH D E ET AL: "OXCARBAZEPINE IN AFFECTIVE AND SCHIZOAFFECTIVE DISORDERS" PHARMACOPSYCHIATRY, GEORG THIEME VERLAG, STUTTGART, DE, vol. 34, no. 6, 2001, pages 242-250, XP009031819 ISSN: 0176-3679

D6: BENES J ET AL: "Anticonvulsant and Sodium Channel-Blocking Properties of Novel 10,11-Dihydro-5H-dibenz[b,f]azepine-5-carb oxamide Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, 1999, pages 2582-2587,

XP002206156 ISSN: 0022-2623

If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

3. The present application relates to a method for the treatment of affective disorders (**claim 1**), for the treatment of manic symptoms (**claim 7**), and for the maintenance treatment of affective disorders (**claim 8**) which comprises administering a carbamazepine derivative of the specified formula I. **Claim 13** and **14** are drafted in a different format but cover the same scope as claim 1. **Claim 16** is directed to a pharmaceutical composition comprising the same carbamazepine derivative and **claim 17** to a combination which further comprises a compound selected from the group consisting of lithium, divalproex, conventional antipsychotics, atypical antipsychotics, lamotrigine and antidepressants. Finally, **claim 20** is directed to the use of said combination for the preparation of a medicament for the treatment of affective disorders, and **claim 21** to a commercial package comprising said combination together with instructions for simultaneous, separate or sequential use thereof in the treatment of affective disorders.

4. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2))

D2 discloses substituted dihydrodibenzoazepines for the treatment of central nervous disorders, including affective disorders, and is novelty destroying for present claims 1, 8 and 11-16.

D3 discloses the compound BIA 2-093 for the treatment of affective disorders, and is novelty destroying for present claims 1, 8 and 11-16.

D4 discloses the pharmacokinetics of 10-hydroxy-carbazepine in epileptic patients treated with phenobarbitone or valproic acid. This is regarded as novelty destroying for the combinations of claims 17, 19 and 21 (the presence of written instructions is not regarded as a distinguishing feature over the corresponding pharmaceutical composition).

5. Furthermore, the present application does not meet the requirements of the PCT with respect to inventive step (Art. 33(3))

D5, which is regarded as the closest prior art, discloses the the use of the anticonvulsant oxcarbazepine (OCBZ) for treating mania in affective and schizoaffective disorders. The present application differs from **D5** in that the carbamazepine derivative is not the ketone but the 10-monohydroxy derivative or esters thereof. Thus, the problem to be solved by the present application is regarded as the provision of alternative carbamazepine derivatives for the treatment of affective disorders.

The *solution* provided by the present application is rendered obvious by **D6**. This document discloses the anticonvulsant properties of the alcohol as well as the esters derivates and proposes their therapeutic use as prodrugs of the active metabolite of oxcarbazepine, the monohydroxy derivate. Thus the skilled person would consider the derivates disclosed in **D6** as an obvious alternative to OCBZ for the therapeutic indications disclosed in **D5**.

In the light of **D5**, combinations of the compounds with the therapeutic agents of claims 17-21 would be also obvious as far as no surprising or advantageous effect arises from the combination.

6.1. Claims 16-19 and 21 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

6.2. For the assessment of the present claims 1-15 and 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment (present claims 1-13 and 15), but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

7. Certain published documents

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/EP2004/003590

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim) (day/month/year)*
WO03/042182	22/05/2003	11/11/2002	12/11/2001